PATENT
MSB-7232

I, Luajuana Riley, do hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail on the date indicated below and is addressed to the Commissioner of Patents and Trademarks, Washington, D. C. 20231.

Luajuana Riley

February 17, 1997
Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: WILLIAM R. ALONSO

Serial No.: 08/532,211

Filed: September 22, 1995

Title: PREPARATION OF VIRALLY INACTIVATED
INTRAVENOUSLY INJECTABLE IMMUNE
SERUM GLOBULIN

APPEAL BRIEF

EXAMINER: Y. EYLER

ART UNIT: 1806

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

This is a Brief (3 copies) supporting an appeal from the final rejection mailed July 17, 1996. Authorization is hereby given to charge deposit account 03-4000 the $300.00 Brief Filing Fee under 37 CFR 1.17(f).

(1) REAL PARTY IN INTEREST: The real party in interest is the designated assignee of the application, Bayer Corporation.

(2) RELATED APPEALS AND INTERFERENCES: There are no related Appeals or Interferences regarding the Application.

(3) STATUS OF CLAIMS: Claims 1 through 24, the only claims pending, stand under final rejection. These claims are shown in the attached Appendix.

PAGE 251

PATENT
MSB-7232

(4) STATUS OF AMENDMENTS: An Amendment after Final Rejection was requested. The Examiner advised that the requested amendments would be entered upon the filing of a Notice of Appeal and this Appeal Brief. That amendment is reflected in the claims of the Appendix.

(5) SUMMARY OF INVENTION: The invention is a method of reducing undesirable anticomplement activity (ACA) resulting from the use of a trialkylphosphate for viral inactivation of a solution of antibodies. The method comprises contacting the solution with the trialkylphosphate under conditions assuring viral inactivation and resulting in an increase in ACA and then incubating the solution under controlled conditions of time, pH, temperature, and ionic strength such that the anticomplement activity is reduced to an acceptable level for intravenous administration of the solution of antibodies. An acceptable ACA level for intravenous administration depends on the antibody concentration. See page 9, lines 14-23 and claims 2-6. The steps of the invention are described in more detail in the Abstract, the Summary of Invention on page 3, lines 8-20 and the claims.

(6) ISSUES: Whether claims 1, 3-6, 10, 21 and 23 should stand rejected under 35 U.S.C. § 112 as vague and indefinite.

Whether claims 1 through 24 should stand rejected under 35 U.S.C. § 103 as unpatentable over Tenold (U.S. 4,396,608) in view of Neurath et al. (U.S. 4,540,573), Mitra et al. (U.S. 4,762,714) and Joy Yang et al. (Vox Sang. 67:337).

(7) GROUPING OF CLAIMS: Claims 1-20 are directed to the method of the invention and stand separate from product by process claims 21-24.

-2-

PAGE 252

(8) <u>ARGUMENTS</u>:

<u>REJECTIONS UNDER 35 U.S.C. § 112 (second paragraph)</u>: Claims 1, 3-6, 10, 21 and 23 were rejected as vague and indefinite in use of the expression, "a given increased level of anticomplement activity". Since the word "given" no longer appears in the claims due to entry of the requested amendment after final, the only issue remaining is whether use of the word "increased" is vague and indefinite on the ground there is no standard against which an increase may be measured. It is respectfully submitted that the "standard" in this application would be the starting ACA level. Since step (a) of the claimed methods results in an increase in ACA from the starting material, a standard is provided. If there is no such increase, then step (b) of the invention, and the invention itself, is not even needed. To illustrate this "standard", the applicant provided in his response of May 9, 1996, a marked up copy of the figure and referred to Table 1 on page 11 to show the "standard" used in that example. A copy of that marked up figure is enclosed with this Brief.

The examiner also objected to the designation of "wt./wt." in claims 3-6, 21, and 23 on the ground it was unclear what the wt./wt. referred to. It is clear from the application and examples that the invention is concerned with treating an <u>aqueous solution</u> of antibodies. Thus, the wt./wt. designation refers to the weight of antibodies (or protein) in a given weight of solution, expressed in a percent basis as is conventional in the art. Basis for an --aqueous-- solution can be found in the second full paragraph on page 5. See also page 7, seventh line from the bottom. Thus, the reference to either a 5% or 10% wt./wt. designation of the antibody solutions of claims 3-6, 21 and 23 clearly refers to the weight of antibodies per weight of solution. See also, Fritz and Schenk, <u>Quantitative Chemistry</u>, p. 8 (copy enclosed) for the definition of weight per cent concentration as it is known in the art.

-3-

PATENT
MSB-7232

In view of the amendments and the above arguments, the rejection of claims 1, 3-6, 10, 21 and 23 as being vague and indefinite under 35 USC 112 is improper.

REJECTIONS UNDER 35 USC 103: Although it may have been an obvious step to combine the TNBP viral inactivation teachings of Neurath et al. with the immune globulin of Tenold, this would only result in step (a). There is no suggestion or motivation to take the process one step further by requiring an incubation step (b). The increase in ACA caused by using TNBP in step (a) was unexpected. A combination of the art as suggested by the examiner assumes the ACA increase was expected. There is no evidence to support that assumption.

Even if the ACA increase could have been expected, it would not have suggested the claims. The claimed invention requires that the conditions pH, temperature and ionic strength of step (b) be selected to reduce the ACA to an acceptable level for IV administration. As pointed out on page 9, an acceptable level of ACA will depend on the weight of protein in the solution that is being treated. There is no evidence the prior art even recognized the problem, much less the solution to the problem as described in the claims. Thus, the combination of selected portions of Tenold and Mitra with the viral inactivation of Neurath et al. and Joy Yang et al. requires the use of hindsight. This is clearly impermissible to support a rejection under 35 USC 103.

In the enclosed revised Figure (submitted earlier only to help understand the invention and not for purposes of being a Formal Drawing), the increased ACA observed when using the viral inactivation technique of Neurath et al. (see middle bar) was surprising. It was only by the applicant's discovery of the unexpected increase of ACA caused by step (a) that the follow up of step (b) was possible. In other words, if the immune globulin of Tenold were simply combined with the viral inactivation of Neurath et al., one skilled in the art would not have even expected the rise in ACA, much less discovered a way to reduce it.

—4—

PAGE 254

PATENT
MSB-7232

The examiner states that Tenold and Mitra et al. teach the reduction of ACA by incubation under controlled pHs, temperature, and tonicity for an extended period of time. Tenold teaches a formulation of IgG which yields a preparation already having low ACA which is stable for at least six months. Tenold does not teach how to obtain a decrease in ACA. Moreover, Tenold describes IgG aggregation as causing ACA. In the present invention, lowering of ACA was not due to decreased IgG aggregates because the TNBP/cholate treated IGIV preparations already contained low levels of aggregated IgG (as measured by HPLC) prior to incubation step of the invention.
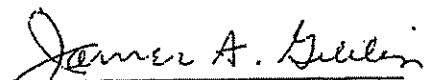
Mitra et al. describe the antiviral action of incubation for at least 3 days at pH 4.25, low ionic strength, and 27°C. However, these authors do not disclose a lowering of IgG ACA due to such incubation conditions. Mitra et al. would not have recognized that TNBP treatment caused an increase in ACA and, by teaching a viral inactivation without chemical agents such as TNBP actually teach away from the claims.

In view of the above remarks, appellants respectfully urge that the rejection of claims 1 through 24 as being obvious under 35 U.S.C. § 103 was improper.

Respectfully submitted,

Dated: _February 17, 1997_

James A. Giblin
Attorney for Applicant
Reg. No. 25,772
Bayer Corporation
800 Dwight Way
P.O. Box 1986
Berkeley, CA 94701
(510) 705-7910

-5-

PATENT
<u>MSB-7232</u>

APPENDIX: CLAIMS

What is claimed is:

1. A method of treating a solution of antibodies which may have virus activity, the method comprising

    a) contacting the solution with a trialkylphosphate and a detergent under conditions sufficient to substantially reduce any virus activity and resulting in an increased level of anticomplement activity; and

    b) then incubating the solution of step a) under conditions of controlled time, pH, temperature, and ionic strength, such that the increased anticomplement activity of the solution is reduced to an acceptable level suitable for intravenous administration.

2. The method of claim 1, wherein the anticomplement activity is reduced to less than about 60 CH_{50} units/mL.

3. The method of claim 1, wherein the solution comprises about 5% wt./wt. antibody and the anticomplement activity is less than about 45 CH_{50} units/mL.

4. The method of claim 3, wherein the solution comprises about 5% wt./wt. antibody and the anticomplement activity is less than about 30 CH_{50} units/mL.

5. The method of claim 1, wherein the solution comprises about 10% wt./wt. antibody and the anticomplement activity is less than about 60 CH_{50} units/mL.

6. The method of claim 5, wherein the solution comprises about 10% wt./wt. antibody and the anticomplement activity is less than about 45 CH_{50} units/mL.
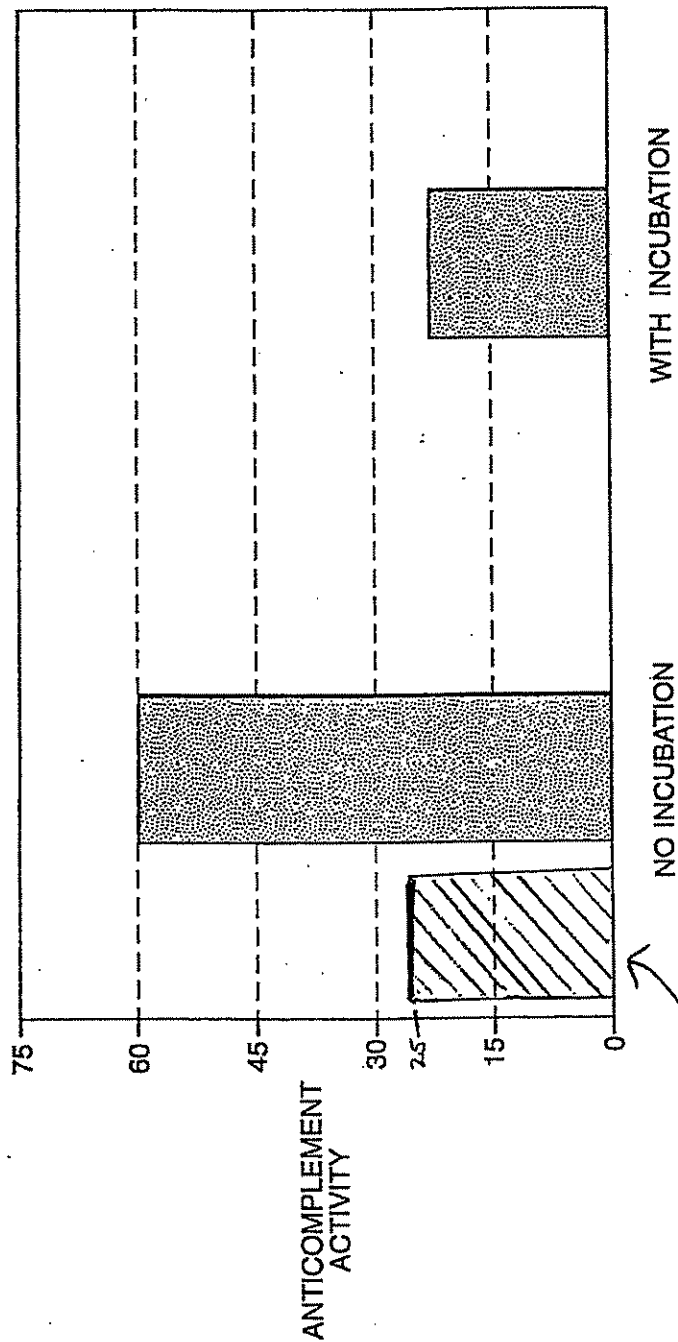
-1-

7. The method of claim 1, wherein the incubation is for at least about ten days.

8. The method of claim 1, wherein the pH is maintained within a range of about 3.5 to about 5.0.

9. The method of claim 1, wherein the temperature is maintained within a range of 2° C to 50° C.

10. The method of claim 1, wherein the ionic strength is less than about 0.001 M.

11. The method of claim 1, wherein at least about 99% of the antibodies are monomeric.

12. The method of claim 1, comprising the further step of adjusting the tonicity of the solution to a physiologic value under such conditions that the ionic strength is not appreciably altered.

13. The method of claim 12, wherein the tonicity of the solution is adjusted by adding a carbohydrate to the solution.

14. The method of claim 13, wherein the carbohydrate used is maltose.

15. The method of claim 12, wherein the tonicity of the solution is adjusted to a range of about 230 to about 490 mosmol/kg solvent.

16. The method of claim 15, wherein the tonicity of the solution is adjusted to a range of about 274 to about 309 mosmol/kg solvent.

17. The method of claim 12, wherein the tonicity of the solution is adjusted by adding an amino acid to the solution.

-2-

PATENT
MSB-7232

18. The method of claim 17, wherein the amino acid used is glycine.

19. The method of claim 1, wherein the trialkylphosphate is tri-n-butyl phosphate and the detergent is selected from polysorbate 80 and sodium cholate.

20. The method of claim 1, wherein the solution has a pH between about 5.5 and about 6.0 during step a).

21. An intravenously injectable immune serum globulin preparation produced by the method of claim 1 and substantially free of lipid enveloped viruses, wherein the preparation has an ionic strength less than about 0.001 M, a pH between about 3.5 and about 5.0, an antibody concentration of about 5% wt./wt., and a maltose concentration of about 10% wt./wt.

22. The preparation of claim 21, wherein the pH is about 4.25.

23. An intravenously injectable immune serum globulin preparation produced by the method of claim 1 and substantially free of lipid enveloped viruses, wherein the preparation has an ionic strength less than about 0.001, a pH between about 3.5 and about 5.0, an antibody concentration of about 10% wt./wt., and a glycine concentration of about 0.2 M.

24. The preparation of claim 23, wherein the pH is about 4.25.

-3-

PAGE 258

MSB-7232

1 / 1

ANTICOMPLEMENT ACTIVITY

75
60
45
30
25
15
0

NO INCUBATION

WITH INCUBATION

Control (Tenold)
See Table 1, page 11.

19/7/1   (Item 1 from file: 149)
DIALOG(R)File 149:IAC(SM) Health & Wellness DB(SM)
(c)1996 Inform Access Co. All rts. reserv.

01493499   SUPPLIER NUMBER: 15900907   (THIS IS THE FULL TEXT)
Safety and cost-effectiveness of solvent-detergent-treated plasma: in
  search of a zero-risk blood supply.
AuBuchon, James P.; Birkmeyer, John D.
JAMA, The Journal of the American Medical Association, v272, n15, p1210(5)
Oct 19, 1994

TEXT:
        Concern about transfusion-transmitted diseases, especially acute
since the appearance of human immunodeficieney virus (HIV), has driven a
growing number of measures aimed at improving the safety of transfusion
therapy. These include supplemental health history questions asked of
potential donors, additional laboratory tests for bloodborne infectious
diseases, and widespread implementation of blood conservation measures,
such as preoperative autologous blood donation. While such efforts have
been remarkably successful in reducing the risks of transfusion-acquired
disease,[1] many have come at substantial cost. For example, preoperative
autologous donation has been estimated to cost between $200 000 and $2
million for each year of life saved.[2,3]
        Solvent-detergent (SD) treatment of frozen plasma (FP) is a new
technology aimed at reducing risks of plasma transfusion still further. The
process, currently under review for licensure by the Food and Drug
Administration, has been projected as eliminating transmission of HIV,
hepatitis B virus (HBV), and hepatitis C virus (HCV) by plasma.[4-9] The
process,[4,10-14] already used in several European countries since 1990,
begins with pooling multiple ABO-identical units of plasma derived from
whole-blood donations. Each pool (300 to 1250 L, derived from 1200 to 5000
donations) is then treated with a solvent-detergent combination
(tri-n-butyl phosphate and Triton X-100 [octyl phenyl-poly-ethylene glycol
ether]) that strips the lipid envelope from enveloped viruses during an
incubation period. These reagents are extracted into soybean oil before
hydrophobic chromatography. The plasma then undergoes sterile filtration
and is packaged in plastic bags as standardized 200-mL units and refrozen.
The composition of SD FP appears similar to regular FP except that about
10% to 15% of procoagulant activity is lost during processing, protein S
and [alpha.sub.2]-antiplasmin levels are slightly decreased, and the larger
multimers of von Willebrand's factors are absent.[10] The residual levels
of the reagents used are believed to be well below toxic levels.[11]
        While SD FP appears promising, there are two potential problems with
the implementation of SD FP. First, the SD process is complex and is
expected to add considerably to the cost of plasma. Second, SD FP may
create new risks. Since the treatment process requires pooling units from
several thousand donors, SD FP may substantially increase the risks of
infection by nonenveloped viruses, such as hepatitis A and parvovirus, or
by pathogens yet to be discovered.
        Since 2.2 million units of plasma are transfused annually in the
United States,[15,16] the widespread implementation of SD FP has
significant public health and economic implications. In this report, we
used decision analysis to estimate the expected benefit and
cost-effectiveness of this new technology.
        MATERIALS AND METHODS
        We modified a previously published Markov decision analysis
model[2,3] to represent transfusion-related outcomes in large, hypothetical

PAGE 260

cohorts of patients undergoing plasma transfusion (SD FP vs non-SD FP). In the model, patients experience in-hospital mortality due to their underlying clinical conditions and (in survivors) transfusion-related complications according to assigned probabilities. Recipients of non-SDd FP face risks of infection with lipid-enveloped viruses (HIV, HBV, and HCV). While we assumed that recipients of SD FP were not susceptible to infection with these viruses (ie, the SD treatment had 100% efficacy), we considered the potential for increased risk of nonenveloped virus transmission to SD FP recipients due to the pooled nature of the SD FP component in a secondary analysis. Each possible clinical outcome in the model is assigned a cost and a utility (in terms of quality-adjusted life expectancy). By considering a large number of hypothetical patients, the model calculates the net cost (per unit) of SD FP as the difference in average transfusion-related costs between SD FP recipients and non-SD FP recipients. Similarly, the model calculates the net benefit of SD FP as the difference in quality-adjusted life expectancy between SD FP recipients and non-SD FP recipients. Cost-effectiveness is then calculated as the ratio of net cost to net benefit.

In calculating net transfusion-related costs, the model incorporates costs associated with the SD treatment process as well as those of treating patients with transfusion-related infectious complications. We estimated the incremental cost of the SD process to be $20 per unit, although we varied this value widely in sensitivity analysis ($0 to $40) to reflect uncertainty in this estimate before its licensure. The methods and data used to estimate the expected lifetime costs of treating transfusion-related infection with HIV, HBV, and HCV have been described in detail in previous analyses.[2,3] In brief, the model accounts for the costs of evaluation and management associated with acute and chronic post-transfusion hepatitis. It also incorporates the considerable costs associated with HIV infection and the acquired immunodeficiency syndrome (AIDS).[17,18]

The net benefit of SD FP was calculated as the difference in quality-adjusted life expectancy predicted for hypothetical cohorts of patients receiving SD FP or non-SD FP. To estimate short-term mortality in FP recipients in the model, we reviewed the records of 63 consecutive patients receiving FP at our medical center during a 3-month period (October to December 1993) (Table 1). Complete records were available for 61 of these. The mean age of these patients was 69 years, and in-hospital mortality was high: 39% (24 of 61 patients). While we used this experience in our baseline estimate of SD FP cost-effectiveness, we considered the possibility of different case mixes of FP recipients at other centers and other protocols for FP transfusion and so assessed cost-effectiveness at different ages and short-term mortality rates. Also, this sensitivity analysis was designed to allow inferences on SD FP cost-effectiveness in specific, different clinical scenarios.

[TABULAR DATA OMITTED]

For the baseline analysis, we used an incidence rate of 0.03% per FP unit (one per 3300 units) for HCV infection.[19-22] The risk of HBV transmission has been estimated at 0.002% per unit (one per 50000 units).[23] The risk of HIV transmission has been estimated to vary from one per 36000 units to one per 250000 units.[24-27] We used a rate of 0.001% (one per 100 000 units) for our baseline analysis. Each incidence rate was tested over broad ranges in sensitivity analysis.

Markov models of prognosis were used to estimate long-term survival for patients with and without transfusion-related complications.[28] In a Markov model, hypothetical patients make transitions between defined health states and accumulate life expectancy, adjusted for the quality of life of each clinical condition, until the health state "death" is reached. Life

PAGE 261

expectancy, or average longevity, is determined by the defined transition probabilities, which is in turn based on baseline and disease-specific mortality rates. Baseline mortality rates, adjusted for age, sex, and race, were obtained from US vital statistics data.[29] To estimate survival in patients infected with HIV, we adapted a four-state Markov model of prognosis with HIV infection reported by Longini et al.[30] To estimate long-term survival in patients with chronic posttransfusion hepatitis, we used an excess mortality rate of 0.35% per year.[2,3]

The model assumes that the chance of transmitting plasma-borne lipid-enveloped viruses (HIV, HBV, and HCV) is eliminated by use of SD FP and, since they are highly cell associated, that human T-cell lymphotropic virus and cytomegalovirus are not transmitted by FP.[31,32] Other consequences of plasma transfusion, such as urticarial reactions, transfusion-related acute lung injury, and hemolysis due to passive transfer of red cell alloantibodies, are assumed to be equally likely with transfusion of both types of FP. The model also assumes that a unit of SD FP is therapeutically equivalent to a unit of non-SD FP.

For calculations of SD FP cost-effectiveness, we did not consider the effects of creating large plasma pools with the potential for transmitting nonenveloped viruses not inactivated by SD treatment. While this risk was assumed to be zero in the baseline analysis, the model was later used to calculate the threshold risk of nonenveloped viral transmission that would negate the aggregate benefits of reducing the risks of HCV, HBV, and HIV transmission. This value was determined under the following assumptions: a pool size of 1000 L (equivalent of 4000 SD FP units) is processed through the SD treatment; the virus results in infection in 50% of patients receiving a transfusion of plasma containing it; and viral infection reduces life expectancy by 50%. (While such a nonenveloped virus with the potential for blood-borne transmission is not currently known to exist, its properties have been hypothesized to resemble those of HIV.)

Cost-effectiveness was assessed from the hospital perspective. Discounting was performed at 5% per year to convert future costs to current value. Because benefits were estimated relative to dollars, both costs and benefits were discounted for calculations of cost-effectiveness.[33] Decision Maker software (Decision Maker 7.0,1991) was used for modeling and analysis.34 All costs were estimated in 1992 dollars.

RESULTS

In our baseline analysis, the use of SD FP extended patient longevity quality adjusted) by approximately 35 minutes per SD FP unit transfused. In other terms, patient longevity was increased by 1 year for every 14 988 SD FP units transfused. This small calculated benefit is attributable largely to the already low rates of HIV, HBV, and HCV transmission by untreated plasma. This benefit of SD FP is achieved at a net cost of $19.30 per unit. That is, the cost of the SD FP treatment process ($20 per unit in the baseline analysis) was minimally defrayed by the expected savings associated with eliminating lipid-enveloped viral infection (70 cents per unit, discounted).

Projecting these cost and benefit estimates to the 2.2 million units of plasma transfused annually in the United States,[14,15] use of SD FP would save 147 quality-adjusted life-years (QALYs) at a cost of $42.5 million annually. Thus, in our baseline analysis, the cost-effectiveness of SD FP was projected to be $289 300 per QALY saved.

In sensitivity analysis, the predicted cost-effectiveness of SD FP was found to be most dependent on estimates of the cost of the plasma treatment process (Figure). The cost per QALY saved by SD FP exceeded $100000 for treatment process costs greater than $7.37 per unit. The cost-effectiveness of SD treatment drops to $50000 per QALY saved (often used as a benchmark for cost-effectiveness) only when treatment process

costs are reduced to $4.04 per unit. The model was less sensitive to varying estimates of the costs associated with treating transfusion-related viral infections. For example, increasing all costs associated with managing HCV, HBV, and HIV infection by five-fold improved the cost-effectiveness estimation of SD FP by only 14% ($289300 to $247300 per QALY saved in the baseline analysis). These costs would have to be 17 times those used in our baseline analysis to make the use of SD FP a cost-savings measure.

The high cost per QALY saved by SD FP estimated in our baseline analysis was in part related to the advanced age (69 years) and high in-hospital mortality (39%) observed in patients receiving plasma at our institution. Replacing the actual short-term mortality observed with an assumption of no risk of in-hospital death improves the estimated cost-effectiveness to $172400 per QALY saved. We also considered SD FP cost-effectiveness for younger and healthier plasma recipients, for whom the sequelae of chronic transfusion-related infections may be more important (Table 2). For example, in 20-year-old trauma patients (hypothetical immediate mortality, 5%), SD FP cost-effectiveness improved to $59000 per QALY saved.

[TABULAR DATA OMITTED]

In cost-effectiveness analysis, we assumed that there were no untoward consequences of using SD FP. However, because the technique requires the pooling of thousands of units of plasma and does not inactivate nonenveloped viruses, there is a potential risk of transmitting a nonenveloped virus to a large number of recipients through this process. Under the assumptions previously described, we calculated that the health benefits in terms of increased quality-adjusted life expectancy) associated with eliminating HBV, HCV, and HIV transmission were entirely negated if the prevalence of nonenveloped virus infection exceeded one per 71 million blood donors.

COMMENT

Reducing viral transmission risk is an important goal of transfusion medicine, and the SD treatment process offers this prospect for more than 2 million units of plasma transfused annually in this country. When viewed from an economic perspective, however, SD FP provides relatively small health benefits at high societal cost. The small average benefit, estimated to be less than 1 hour in life expectancy per unit transfused in our baseline analysis, is largely attributable to the diminishing risks of enveloped virus transmission from untreated plasma. The risks of HIV, HBV, and HCV have decreased by at least 10-fold during the last decade,[1] and further improvements may occur. The calculated benefit of SD FP is also small because plasma recipients tend to be elderly and have high short-term mortality rates from their underlying clinical conditions. For these patients, the benefits of avoiding chronic transfusion-related infections are proportionately less.

Because retrospective and prospective reviews of all component transfusion requests at this institution may have reduced FP usage lower than that experienced at other institutions,[35,36] we anticipated more frequent FP transfusion (and thus transfusion to patients with improved short-term survival chances) in the hypothetical scenarios analyzed than those in the baseline analysis. Our baseline estimate of the cost-effectiveness of SD FP was $289300 per QALY saved. While many of the parameters used in the analysis were necessarily imprecise, the cost-effectiveness of SD FP generally exceeded $100000 per QALY saved when the important variables in the model were allowed to vary over plausible ranges in sensitivity analysis and when SD FP's use was analyzed in various hypothetical scenarios.

While there is no consensus on a dollar amount that established a

PAGE 263

JA263

clinical practice as cost-effective, SD treatment of FP (as a preventive measure) does not compare favorably with many common therapeutic medical interventions as a public health investment. For example, coronary artery bypass graft surgery, hemodialysis, and cardiac transplant cost less than $50000 per QALY saved.[37-39] Only in situations where SD FP would be transfused to younger adults with a low probability of short-term mortality is this threshold approached. Comparing SD treatment of FP to other preventive strategies, this approach is more expensive, for example, than the use of Papanicolaou tests to detect early cervical cancer (approximately $10000 per QALY saved)." The cost-effectiveness of SD FP is similar to that of preoperative autologous donation that yields one QALY saved for expenditures of $50000 to $2 million, depending on the clinical situation.[2,3]

Our analysis may have underestimated the true costs associated with SD FP. First, each 200-mL unit of SD FP has only approximately 80% of the procoagulants usually found in a regular 220- to 240-mL unit of FP.[10] If SD FP transfusions are ordered on the basis of procoagulant activity rather than on set formulas, our assumption that units of SD FP and non-SD FP are therapeutically equivalent may have underestimated the costs of providing this form of plasma by approximately 20%. Second, and perhaps more importantly, the analysis did not account for potential increases in plasma utilization due to the availability of SD FP. Frozen plasma use is often discretionary, and there is already considerable variability in its use among institutions and physicians.[41] The availability of plasma that is perceived to be risk-free would no doubt lower the threshold of many physicians for using this blood product in borderline situations, thus increasing overall transfusion costs without clear benefits.

Our estimates of the cost-effectiveness of SD FP are only as precise as the costs used in the analysis. Since SD FP has not yet been licensed by the Food and Drug Administration, the cost of the process cannot be obtained directly. Our baseline estimate ($20 per unit) was based on a consensus of several blood bank experts, but it is conceivable that this value could decrease over time with widespread implementation and increasing efficiency of the SD process. However, for SD FP to be cost-effective (less than $50000 per QALY saved), its costs would have to decrease approximately fivefold, to $4.04 per unit. It is also difficult to estimate the costs of treating transfusion-related infections. For a variety of methodological reasons, the costs used in this analysis and previous studies by Birkmeyer et al[2,3] differ from those used in other analyses.[42,43] However, it is important to note that SD FP cost-effectiveness was minimally sensitive to the costs of treating transfusion-related complications: increasing all such costs in the model by fivefold improved estimated cost-effectiveness by only 14%.

The need to pool large numbers of plasma units is a significant disadvantage of the SD treatment process. While SD FP should offer protection against as-yet-unidentified lipid-enveloped viruses, the pooling process substantially increases the transmission risks of potential pathogens not affected by the treatment. Theoretically, a nonenveloped virus from a single donor could be transmitted to several thousand recipients. Of the known nonenveloped viruses, there is debate whether antibodies against hepatitis A virus in a plasma pool would prevent transmission of this virus. Although residual detectable antibodies to hepatitis A virus in the final SD FP component suggest that transmission is unlikely,[10] there have been reports of transmission of hepatitis A to hemophiliacs through SD-treated antihemophilic factor.[44,45] Parvovirus B19 antigen or genetic sequences have been found in one per 5000 to one per 24 000 blood donors,[46,47] and the virus has been reported to be transmitted through SD-treated antihemophilic factor.[48] The extent to

which transmission of parvovirus B19 would cause morbidity in SD FP recipients is unknown, although infection with this virus can be life threatening in some patients.[49,50] At present, many issues about nonenveloped viruses remain unknown, including prevalence rates in blood donors, the efficiency at which these viruses are transmitted by transfusion, and their clinical effects. In sensitivity analysis, however, we found that even minute risks of nonenveloped virus transmission (one per 71 million donors under several broad assumptions) using SD FP were sufficient to negate the benefits of eliminating the risks of HBV, HCV, and HIV infection, which are transmitted from one donor to only one recipient with non-SD FP. Such small risks could not be detected by usual epidemiologic surveillance systems.

Transfusion medicine specialists are caught between two strong, competing pressures. On the one hand, media reports and public concerns about transfusion risks since the appearance of HIV and mounting liability concerns continue to drive the blood banking system toward a goal of a zero-risk blood supply. On the other hand, recognition that health care resources are limited requires that blood bankers control costs. Also, most acknowledge that a completely zero-risk blood supply is not attainable.[51] The case of SD FP highlights this conflict. While encouraging in its potential to reduce transfusion-related infections, the benefits of SD FP come at substantial cost, providing considerably less benefit for the resources required than most accepted medical practices. If SD FP were approved by the Food and Drug Administration, health care providers and payers will have to consider these difficult tradeoffs when deciding about broad implementation of this new technology.

We gratefully acknowledge the advice and comments of Benjamin Littenberg, MD.

References

[1.] Dodd RY. The risk of transfusion-transmitted infection. N Engl J Med. 1993;327:419-421. [2.] Birkmeyer JD, Goodnough LT, AuBuchon JP, Noordsij PG, Littenberg B. The cost-effectiveness of preoperative autologous blood donation in total hip and knee replacement. Transfusion. 1993;33: 544-551. [3.] Birkmeyer JD, AuBuchon JP, Littenberg B, et al. The cost-effectiveness of preoperative autologous donation in coronary bypass surgery. Ann Thorac Surg. 1994;57:161-169. [4.] Piet MP, Chin S, Prince AM, et al. The use of tri-(n-butyl) phosphate detergent mixtures to inactivate hepatitis viruses and human immunodeficiency virus in plasma and plasma's subsequent fractionation. Transfusion. 1990;30:591-598. [5.] Wiedung JU, Hellstern P, Kohler M. Inactivation of viruses in fresh-frozen plasma. Ann Hematol. 1993;67:259-266. [6.] Edwards CA, Piet MPJ, Chin S, et al. Tri(n-butyl) phosphate/detergent treatment of licensed therapeutic and experimental blood derivatives. Vox Sang. 1987;52:53-59. [7.] Horowitz B, Wiebe ME, Lippin A, et al. Inactivation of viruses in labile blood derivatives, I: disruption of lipid-enveloped viruses by tri(n-butyl) phosphate detergent combinations. Transfusion. 1985;25:516-522. [8.] Horowitz B, Wiebe ME, Lippin A, et al. Inactivation of viruses in labile blood derivatives, II: physical methods. Transfusion. 1985;25:523-527. [9.] Horowitz B. Blood protein derivative viral safety: observations and analysis. Yale J Biol Med. 1990; 63:361-369. [10.] Horowitz B. Viral safety and biochemical characterization of S/D *plasma*. In: FDA Workshop: The Role of Virus Inactivated Plasma in Clinical Medicine. Bethesda, Md: Food and Drug Administration; March 24, 1994. [11.] Leuschner J. The toxicology of *TNBP* and Triton X-100. In: FDA Workshop: The Role of *Virus* Inactivated *Plasma* in Clinical Medicine. Bethesda, Md: Food and Drug Administration; March 24,1994. [12.] Horowitz B, Bonomo R, Prince AM, Chin SN, Brotman B, Shulman RW. Solvent/detergent-treated plasma: a virus inactivated substitute for fresh frozen plasma. Blood. 1992;79:826-831.

[13.] Hellstern P, Sachse H, Schwinn H, Oberfrank K. Manufacture and in vitro characterization of a solvent/detergent-treated human plasma. Vox Sang. 1992;63:178-185. [14.] Piquet Y, Janvier G, Doutremepuich C, et al. Virus inactivation of fresh frozen plasma by a solvent-detergent procedure: biological results. Vox Sang. 1992;63:251-256. [15.] Surgenor D. Demographic data on use of FFP. In: FDA Workshop: The Role of Virus Inactivated Plasma in Clinical Medicine. Bethesda, Md: Food and Drug Administration; March 24, 1994. [16.] Wallace EL, Surgenor DM, Hao HS, AnJ, Chapman RH, Churchill WH. Collection and transfusion of blood and blood components in the United States, 1989. Transfussion. 1993;33:139-144. [17.] Hellinger FJ. Updated forecasts of the costs of medical care for persons with AIDS, 1989-1993. Public Health Rep. 1990;105:1-12. [18.] Arno PS, Shenson D, Siegel NF, Franks P, Lee PR. Economic and policy implications of early intervention in HIV disease. JAMA. 1989;262:1493-1498. [19.] Donahue JG, Munoz A, Ness PM, et al. The declining risk of post-transfusion hepatitis C virus infection. N Engl J Med. 1992;327:369-373. [20.] Contreras M, Barbara JA, Anderson CC, et al. Low incidence of non-A, non-B post-transfusion hepatitis in London confirmed by hepatitis C virus serology. Lancet. 1991;337:753-757. [21.] Dodd RY. Will blood products be free of infectious agents? In: Nance ST, ed. Transfusion Medicine in the 1990's. Arlington, Va: American Association of Blood Banks; 1990:223-251. [22.] Van der Poel CL, Reesink HW, Schaasberg W; et al. Infectivity of blood seropositive for hepatitis C virus antibodies. Lancet. 1990;335:558-560. [23.] Centers for Disease Control. Public Health Service interagency guidelines for screening donors of blood, plasma, organ, tissues, and semen for evidence of hepatitis B and hepatitis C. MMWR Morb Mortal Wkly Rep. 1991;40:1-17. [24.] Menitove JE. Current risk of transfusion-associated human immunodeficiency virus infection. Arch Pathol Lab Med. 1990;114:330-334. [25.] Busch MP, Eble BE, Khayam-Baashi H, et al. Evaluation of screened blood donations for human immunodeficiency virus type 1 infection by culture and DNA amplification of pooled cells. N Engl J Med. 1991;325:1-5. [26.] Cumming PD, Wallace EL, Schorr JB, Dodd RY. Exposure of patients to human immunodeficiency virus through the transfusion of blood components that test antibody-negative. N Engl J Med. 1989;321:941-946. [27.] Nelson KE, Donahue JG, Munoz A. Transmission of retroviruses from seronegative donors by transfusion during cardiac surgery: a multicenter study of HIV-1 and HTLV-I/II infections. Ann Intern Med. 1992;117:554-559. [28.] Beck JR, Pauker SG. The Markov process in medical prognosis. Med Decis Making. 1983,3:419-458. [29.] National Center for Health Statistics. Vital Statistics of the United Stated, 1987: Mortality, Part A. Washington, DC: Public Health Service; 1987;2:8. [30.] Longini IM Jr, Clark WS, Byers RH, et al. Statistical analysis of the stages of HIV infection using a Markov model. Stat Med. 1989;8:831-843. [31.] Bowden RA, Slichter SJ, Sayers MH, et al. Use of leukocyte-depleted platelets and cytomegalovirus-seronegative red blood cells for prevention of primary cytomegalovirus infection after marrow transplant. Blood. 1991;78:246-250. [32.] AuBuchon JP, Dodd RY. Inactivation of microbial contaminants of blood components. Clin Lab Med. 1992;12:787-803. [33.] Weinstein MC. Clinical Decision Analysis. Philadelphia, Pa: WB Saunders Co; 1980. [34.] Sonnenberg FA, Pauker SG. Decision Maker: an advanced personal computer tool for clinical decision analysis. In: Proceedings of the Eleventh Annual Symposium on Computer Applications in Medical Care. Washington, DC: IEEE Computer Society Press: 1988. [35.] Simon T. Evolution in indications for blood component transfusion. Clin Lab Med. 1992;12:655-667. [36.] Shanberge JN, Quattrociocchi-Longe T. Analysis of fresh frozen plasma administration with suggestions for ways to reduce usage. Transfus Med. 1992;2:189-194. [37.] Weinstein MC, Stason WB. Cost-effectiveness of coronary artery bypass surgery. Circulation.

1982;66(suppl 3):56-66. [38.] Evans RW. Cost-effectiveness analysis of transplantation. Surg Clin North Am. 1986;66:603-616. [39.] Stange PV, Sumner AT. Predicting treatment costs and life expectancy for end-stage renal disease. N Engl J Med. 1978;298:372-378. [40.] Eddy DM. Screening for cervical cancer. Ann Intern Med. 1990;113:214-226. [41.] Goodnough LT, Johnston MFM, Toy PTCY, et al. The variability of transfusion practice in coronary artery bypass surgery. JAMA. 1991;265:86-90. [42.] Hellinger FJ. The lifetime cost of treating a person with HIV. JAMA. 1993;270-474-478. [43.] Bloom BS, Hillman AL, Fendrick AM, Schwartz JS. A reappraisal of hepatitis B vaccination strategies using cost-effectiveness analysis. Ann Intern Med. 1993;118:298-306. [44.] Geritzen A, Schneweis KE, Brackmann H-H, et al. Acute hepatitis A in hemophiliacs. Lancet. 1992;340:1231-1232. [45.] Normann A, Graff A, Gerritzen A, Brackmann H-H, Flehmig B. Detection of hepatitis A virus RNA in a commercially available factor VIII preparation. Lancet. 1992;340:1232-1233. [46.] Cohen BJ, Field AM, Gudnaottir S, Beard S, Barbara JAJ. Blood donor screening for parvovirus B19. J Virol Methods. 1990;30:233-238. [47.] McOmish F, Yap PL, Jordan A, Hart H, Cohen BJ, Simmonds P. Detection of parvovirus B19 in donated blood: a model system for screening by polymerase chain reaction. J Clin Microbiol. 1993; 31:323-328. [48.] Lefrere J-J, Mariotti M, Thauvin M. B19 parvovirus DNA in solvent/detergent-treated anti-hemophilia concentrates. Lancet. 1994;343:211-212. [49.] Anderson LJ, Torok TJ. The current clinical spectrum of human parvovirus B19. Curr Clin Top Infect Dis. 1991;11:261-280. [50.] Centers for Disease Control. Risks associated with human parvovirus B19 infection. MMWR Morb Mortal Wkly Rep. 1989;38:91-97. [51.] Zuck TF. Greetings: a final look back with comments about a policy of a zero-risk blood supply. Transfusion. 1987;27:447-448.
COPYRIGHT 1994 American Medical Association

   Possibilities of *virus* inactivation of pooled fresh *plasma* with tri-n-butylphosphate (*TNBP*) and detergent (SD treatment)
   Guertler L
   Max-von-Pettenkofer-Inst. Hyg. Med. Mikrobiol., Univ. Muenchen, Pettenkoferstr. 9a, D-80336 Muenchen, GER
   Treatment with tri-n-butyl-phosphate and detergent (SD-treatment) leads to efficient inactivation of viruses having a lipid enveloped surface, like hepatitis B virus, hepatitis C virus and human immunodeficiency virus, that are presently the most transfusion relevant viruses in Germany. Other lipid enveloped viruses of the herpes group like cytomegalovirus and Epstein-Barr virus are inactivated as well. Non-enveloped viruses like parvovirus B19 and picornaviruses are not inactivated by SD-treatment. Future inactivation of blood components like plasma and bloodproducts will be a combination of SD- and heat-treatment. Keeping single plasma units in quarantaine for 6 months is one of the alternatives in elevating transfusion safety. For transfused blood the safety against infectious agent will continue to depend on the effectiveness of donor selection and the efficacy of testing.

US PAT NO: 4,617,379 [IMAGE AVAILABLE]   ANS: 1

ABSTRACT:
Normal plasma from donors who have not been vaccinated with a
cytomegalovirus vaccine can be screened for higher than normal titers of
naturally occurring antibody to cytomegalovirus. Those plasmas with high
titers of such antibody can be pooled and fractionated to give
hyperimmune serum globulin. The product may be treated to render it
suitable for intravenous injection. Patients with cytomegalovirus
infection or at risk to such infection, may receive the present product
to raise serum titers of cytomegalovirus antibody.
=>

```
Set       Items    Description
S1         1245    IMMUNE(W)SERUM(W)GLOBULIN
S2          185    S1(20N)VIRUS
S3            0    S2(20N)(ACA OR ANTICOMPLEMENT)
S4           97    REMOVE DUPLICATES S2 (unique items)
S5            0    S1D(20N)ANTI(W)COMPLEMENT?
S6           32    S1(20N)COMPLEMENT
S7           17    REMOVE DUPLICATES (unique items)
S8            1    S1(25N)(TRIALKYL(W)PHOSPATE OR TRI(3W)BUTLY(W)PHOSPATE OR -
                   TNBP)
S9            0    S1(20N)CHOLATE
S10           1    S1(20N)(DETERGENT OR POLYSORBATE OR TWEEN)
S11           1    S10 NOT S9
S12           5    S1 AND TONICITY
S13           5    REMOVE DUPLICATES (unique items)
S14          33    S1 AND IONIC(W)STRENGTH
S15          33    REMOVE DUPLICATES (unique items)
S16     5994733    SERA OR SERUM OR PLASMA OR BLOOD OR BLOOD(W)PRODUCT?
S17      141590    S16(20N)VIRUS
S18          34    S17(20N)(TRIALKYL(W)PHOSPHATE OR TRI(3W)BUTLY(W)PHOSPHATE -
                   OR TNBP)
S19          22    REMOVE DUPLICATES (unique items)
S20        3532    S17(20N)(ANTI(W)COMPLEMENT? OR COMPLEMENT? OR ACA)
S21           7    S20(20N)(INCUBATE OR REDUCE)
S22           5    REMOVE DUPLICATES (unique items)
S23        2565    S17(10N)(ANTI(W)COMPLEMENT? OR COMPLEMENT OR ACA)
S24         236    S17(10N)(ANTI(W)COMPLEMENT? OR COMPLEMENT OR ACA)(5N)ACTIV-
                   ITY
S25         137    REMOVE DUPLICATES (unique items
```

US PAT NO: 3,903,262 [IMAGE AVAILABLE]   L30: 18 of 18
TITLE: Pharmaceutical compositions comprising intravenously
               injectable modified serum globulin, its production and
               use

ABSTRACT:
A pharmaceutical composition comprising, in a pharmaceutically acceptable
aqueous carrier adapted for intravenous administration, an intravenously
injectable, substantially pure modified immune serum globulin consisting
essentially of intact immune serum globulin chains having intact
intrachain disulfide linkages and cleaved at at least one interchain
disulfide linkage, each cleaved disulfide linkage being replaced by a
pair of alkylated mercapto groups, the cleaved chains remaining united by
non-covalent association so that the apparent molecular weight of the
modified serum globulin in non-dissociating solvents is substantially the
same as unmodified immune serum globulin, said modified immune serum
globulin being substantially free from both actual and latent
anti-complement activity and having substantially the biological
half-life and spectrum of antibody activity of corresponding unmodified
immune serum globulin, said modified immune serum globulin having an
$H_2 L_2$ content of less than 7 percent, an $H_2 L_2$ +
$H_2 L$ + H_2 content of 5-30 percent and an HL + H + L content of
95-70 percent wherein H is an intact heavy chain and L an intact light
chain, and having an S-alkylated cysteine content of about 5.6-9.5 moles
per mole of immune serum globulin; said modified immune serum globulin
being produced by selectively reducing a mildly alkaline aqueous solution
of an immune serum globulin with dithiothreitol or dithioerythritol,
alkylating the thus-reduced interchain disulfide groups, and separating
the thus-modified globulin from the non-proteinaceous reaction products.

US PAT NO: 4,136,094 [IMAGE AVAILABLE]   L14: 52 of 57
TITLE: Preparation of intravenous human and animal gamma
                globulins and isolation of albumin

ABSTRACT:
A method of isolating and purifying natural, unaltered, undenatured
immune gamma globulin (IgG) for intravenous administration and albumin
from animal blood plasma, especially human, and the resulting products.
The method involves the initial stabilization of plasma by treatment with
silica, or the use of previously stabilized plasma. IgG and albumin are
isolated from the stabilized plasma by chromatographic reaction with
sterile ion exchange resin and eluted by adjustment of pH and ionic
strength. The products are concentrated, purified further and packaged.
They are characterized by high yield and high purity. They are
unfragmented and unaggregated, i.e., natural preparation.

US PAT NO: 3,986,927 [IMAGE AVAILABLE]   L14: 53 of 57
TITLE: Process for the purification and sterilization of
                acidophilic biologicals by extreme acidification at cold
                temperatures

ABSTRACT:
Methods of sterilizing biologicals in which the biologicals are acidified
to a pH of not higher than about 1.0, preferably 0.75 to about 0.5, and
the acidified biologicals are stored at cold temperatures for a perod of
time sufficient to inactivate microbial flora contained therein but not
the biological itself, for example; in the range of about 0.degree. to
about 10.degree. C for 1-24 hours or longer. Precipitates formed during
the storing are clarified and the biologicals are then neutralized,
preferably to a pH of from about 7.0 to about 8.0, or that pH at which
the biological is best stored, e.g., trypsin at pH 3-4. The methods
include clarifying biologicals of precipitates formed within the first
two to three hours and then continuing the storing and again clarifying
the biologicals of precipitates.
Microbial flora and numerous contaminated proteins contained in the
biologicals are removed resulting in completely sterilized biologicals
retaining initial activity or titer. If desired, the clarified
biologicals may be stored in acidic state since advantageously they reman
biologically stable at ambient temperatures when stored at low pH levels,
and then neutralized shortly before dispensing. A number of examples is
set forth.

US PAT NO: 4,540,573 [IMAGE AVAILABLE]   L14: 44 of 57
TITLE: Undenatured virus-free biologically active protein
                  derivatives

ABSTRACT:
A mammalian blood protein-containing composition such as whole blood,
plasma, serum, plasma concentrate, cryoprecipitate, cryosupernatant,
plasma fractionation precipitate or plasma fractionation supernatant
substantially free of hepatitis and other lipid coated viruses with the
yield of protein activity to total protein being at least 80% is
disclosed. The protein-containing composition is contacted with di- or
trialkylphosphate, preferably a mixture of trialkylphosphate and
detergent, usually followed by removal of the di- or trialkylphosphate.

US PAT NO: 4,820,805 [IMAGE AVAILABLE]   L14: 27 of 57
TITLE: Undenatured virus-free trialkyl phosphate treated
                biologically active protein derivatives

ABSTRACT:
A mammalian blood protein-containing composition such as whole blood,
plasma, serum, plasma concentrate, cryoprecipitate, cryosupernatant,
plasma fractionation precipitate or plasma fractionation supernatant
substantially free of hepatitis and other lipid coated viruses with the
yield of protein activity to total protein being at least 80% is
disclosed. The protein-containing composition is contacted with di- or
trialkylphosphate, preferably a mixture of trialkylphosphate and
detergent, usually followed by removal of the di- or trialkylphosphate.

US PAT NO: 5,110,910 [IMAGE AVAILABLE]   L14: 18 of 57
TITLE: Virucidal euglobulin precipitation

ABSTRACT:
A source for antibodies (both IgG and IgM types) is put into an aqueous
solution which includes a virucidal agent under conditions sufficient to
assure substantially complete dissolution of both the antibodies and the
virucidal agent and virus inactivation. Then the pH, conductivity and
antibody concentration of the solution are then changed to obtain
conditions sufficient to assure the precipitation of substantially all
antibodies while maintaining substantially all of the virucidal agent in
the supernatant solution.
In preferred embodiments, using a TNBP/TWEEN virucidal agent, the
original solution conductivity ranges from about 0.03 to 0.20 M MHO/CM,
the pH ranges from about 4.75 to 4.85, and the protein concentration,
when measured at A280, ranges from a reading of about 5 to 40. In the
second precipitation step, the pH is changed to a range of about 6.0 to
7.5 and the conductivity is changed to a range of about 0.05 to 0.70 M
MHO/CM to achieve an IgM precipitation ranging from about 30 to 80% by
weight total protein.

US PAT NO: 5,132,406 [IMAGE AVAILABLE]   L14: 16 of 57
TITLE: Method of producing immunoglobulin preparations for
               intravenous injection

ABSTRACT:
A method of producing immunoglobulin preparations for intravenous
injection which starts with an immunoblobulin-containing fraction and
comprises the treatment steps of:
(a) treating said fraction with 4-10 weight/volume percent of
 polyethylene glycol having a molecular weight of 1,000-10,000 under
 conditions of pH 4-6, ion strength 0.0001-0.1M and temperature
 0.degree.-4.degree. C. and recovering the supernatant,
(b) treating the supernatant obtained in step (a) with 10-15
 weight/volume percent of polyethylene glycol having a molecular weight
 of 1,000-10,000 under conditions of pH 6-9, ion strength 0.0001-0.1M and
 temperature 0.degree.-4.degree. C. and recovering the resulting
 precipitate, and
(c) heat-treating, in any desired step, said immunoglobulin in the
 presence of a stabilizer under conditions sufficient to inactivate
 contaminant viruses.
The preparations obtained according to the invention retain
immunoglobulins without substantial inactivation thereof, and are
substantially free of such contaminants as anti-human blood group
substance antibodies. With contaminant viruses inactivated as a result of
the heat treatment, said preparations have good solubility and are
sufficiently low in anticomplement activity.

US PAT NO: 5,371,196 [IMAGE AVAILABLE]   L14: 2 of 57
TITLE: Process for producing secretory immunoglobulin A
                preparations

ABSTRACT:
Secretory immunoglobulin A preparations substantially not containing
virus are produced by a process wherein secretory immunoglobulin A which
might be contaminated with viruses is (1) heated about 60.degree. C. for
about 10 hours, or (2) subjected to the reaction with tri-n-butyl
phosphate and a surfactant and the heating as mentioned above, as
liquidized form in an aqueous medium, and then polymerized matters are
precipitated from the resulting solution by adding polyethyleneglycol
thereto.

US PAT NO: 5,288,853 [IMAGE AVAILABLE]   L11: 8 of 21

DETDESC:

DETD(10)

In . . . of this invention, the Factor VIII complex production
process includes steps for inactivating viruses that may be present in
such **blood** **products**, e.g., hepatitis B **virus**, hepatitis
non-A/non-B **virus**, HIV (AIDS **virus**), Cytomegalovirus,
Epstein-Barr **virus**, and the like, prior to the affinity
chromatography step. In one embodiment, a solution comprising both an
organic solvent and a detergent, is added to the PEG supernatant to
inactivate **virus** that may be present. The amount of organic solvent
and detergent added preferably results in a solution comprising about
0.3%. . . another is a detergent sold under the trademark "TRITON
X-100," by Aldrich Company, of Milwaukee, Wis. Useful organic solvents
are **tri**-n-**butyl**-**phosphate** (**TNBP**), ethyl ether, and the
like. The solution is incubated for about 6 hours to about 7 hours, at a
temperature of from about 24.degree. C. to about 30.degree. C.
Inactivation of **virus** using organic solvent/detergent mixture is
described in U.S. Pat. No. 4,540,573, which issued on Sep. 10, 1985 to
Neurath et. . . .

US PAT NO: 5,486,293 [IMAGE AVAILABLE]   L11: 1 of 21

SUMMARY:

BSUM(4)

 Numerous . . . inactivate viruses such as Hepatitis B (HB), non-A,
non-B Hepatitis (NANBH), Human T Lymphotrophic Retrovirus Type 3 (HTLV),
Human Immunodeficiency **Virus** (HIV), and Lymphadenopathy Associated
Virus (LAV). At present, the method of choice for inactivating these
viruses in **blood** and **blood** fractions is treatment with a solvent
such as **tri**-n-**butyl** **phosphate** and a detergent such as
polysorbate 80 (Tween 80) or sodium cholate. Much of the early work in
this area was done by the group of Bernard Horowitz and Alfred Prince at
the New York **Blood** Center and as of February 1991, over 1.7 million
doses of solvent and detergent treated coagulation factor concentrates
had been. . .

averaged between 0.025 and 0.045 C'50 units/mg. In addition, no.   .   .
or no carbohydrates were found to be stable for at least 6 months at both
refrigeration and room temperatures. The **anticomplement** activity did
not change significantly from the initial levels, and averaged between
0.07 and 0.1 C'50 units/mg. As with the.   .   .

22.   4,692,331, Sep. 8, 1987, Gamma-globulin preparation for intravenous
administration; Yahiro Uemura, et al., 424/159.1, 177.1; 530/390.5 [IMAGE
AVAILABLE]

US PAT NO: 4,692,331 [IMAGE AVAILABLE]   L13: 22 of 59

ABSTRACT:
A dry .gamma.-globulin preparation capable of intravenous injection which
is obtainable by polyethylene glycol fractionation of plasma is improved
in its water-solubility and stability against increase of
anticomplement activity and decrease of antibody titer by purifying
the .gamma.-globulin fraction with respect to protein to render the
residual polyethylene glycol substantially not detectable in its 5% w/v
solution, adding 0.2 to 2 parts by weight of glucose based on 1 part of
.gamma.-globulin, and lyophilizing its solution.

ABSTRACT:
A .   .   .   injection which is obtainable by polyethylene glycol
fractionation of plasma is improved in its water-solubility and stability
against increase of **anticomplement** activity and decrease of antibody
titer by purifying the .gamma.-globulin fraction with respect to protein
to render the residual polyethylene.   .   .

SUMMARY:

BSUM(5)

 When .   .   . stability of the .gamma.-globulin against deterioration
with time becomes poor accompanied by the decrease in antibody titer and
increase in **anticomplement** activity. It was found out that this
tendency can be prevented markedly by addition of a sufficient amount of
glucose.   .   .

DETDESC:

DETD(14)

 In .   .   . antibody titer was determined by the hemagglutination
inhibition test and expressed in terms of the international unit (IU/100
mg). The **anticomplement** activity was determined according to Kabatt
and Meyer {Experimental Immunochemistry, 225 (1961)} and Nishioka and
Okada {Men'eki no Seikagaku (Biochemistry.   .   . of a complement was
mixed with a sample to be tested, and the units remaining after
decreasing was measured. The **anticomplement** activity was expressed in
terms of the decrease in units.

DETDESC:

DETD(16)

 A .gamma.-globulin for intravenous administration (measles antibody
titer: 9.2 IU/100 mg, **anticomplement** activity: 15) fractionated by

use of Polyethylene Glycol #4000 was dissolved in a 0.02 M acetate buffer
solution, ph 7.0,. . . at 30.degree. C. for 10 months, the dried
preparation showed neither a decrease in antibody titer nor an increase
in **anticomplement** activity.

DETDESC:

DETD(18)

To . . . lyophilized to obtain a dried preparation. The
.gamma.-globulin solution showed a measles antibody titer of 9 IU/100 mg
and an **anticomplement** activity of 15. No polyethylene glycol was
detected by the colorimetry.

DETDESC:

DETD(19)

The . . . was stored aseptically at 30.degree. C. for 5 days and then
further for 5 months aseptically. The antibody titer and
anticomplement activity were measured after each period. The results
were as shown in the following table. Statistically significant effects
were observed. . .

4. 5,159,064, Oct. 27, 1992, Preparation of virus-free antibodies; Gautam Mitra, et al., 530/388.23; 424/141.1, 176.1, 530; 435/236; 514/2; 530/388.1, 388.25, 388.4, 390.1 [IMAGE AVAILABLE]

US PAT NO: 5,159,064 [IMAGE AVAILABLE]   L13: 4 of 59

ABSTRACT:
Antibodies, including monoclonal antibodies (Mabs), can be made substantially free of infectious viruses by storing them in a liquid state at conditions of pH, temperature and time sufficient to inactive substantially all infectious viruses. Preferred inactivation methods involve use of a pH equal to or less than about 4.0 at a temperature of at least about 5.degree. C. for at least about 16 hours.

SUMMARY:

BSUM(6)

  Initial attempts to render an ISG safe and effective for IV administration (IVIG) focused on eliminating its **anticomplement** activity. In one approach, for example, this involved chemically modifying the ISG (see U.S. Pat. No. 3,903,262 to Pappenhagen et.

21. 4,719,290, Jan. 12, 1988, Composition of intravenous immune globulin; Willie M. Curry, et al., 424/177.1, 159.1, 170.1; 514/2, 6; 530/363, 389.5, 390.5, 419, 861 [IMAGE AVAILABLE]

US PAT NO: 4,719,290 [IMAGE AVAILABLE]   L13: 21 of 59

ABSTRACT:
An intravenous immune globulin preparation having at least 99% pure globulin protein and an **anticomplement** activity of less than 0.10 C'50 units/mg IgG prepared by: precipitating impurities from Cohn Fraction II in an aqueous-alcohol medium at defined temperature and pH, removing the precipitated impurities, stabilizing the diluted solution with albumin, concentrating the solution and removing the alcohol therefrom. Also prepared by this method, an intravenous, hyperimmune globulin preparation having increased antibody titers to sixteen serospecific strains of Pseudomonas aeruginosa.

ABSTRACT:
An intravenous immune globulin preparation having at least 99% pure globulin protein and an **anticomplement** activity of less than 0.10 C'50 units/mg IgG prepared by: precipitating impurities from Cohn Fraction II in an aqueous-alcohol medium.

SUMMARY:

BSUM(9)

  Human . . . the 1940's by F. J. Cohn. It was also observed that the aggregate formed during the fractionation procedure results in **anticomplement** activity and that clinical application causes adverse reactivity in the patient.

SUMMARY:

BSUM(15)

The prior art has made great efforts to prepare immune globulin which has lesser **anticomplement** activity, mainly by decomposing or removing the aggregated or denatured globulin. Such efforts included: enzymatical hydrolysis using pepsin, plasmin, papain,. . .

SUMMARY:

BSUM(16)

While these methods seemed to decrease the presence of aggregated or denatured globulin in the final products and consequently lowered the **anticomplement** activity, they were not without other shortcomings, such as low activity of the antibody, shortened half-life time of the immunoglobulin. . .

SUMMARY:

BSUM(27)

It is still another object of the present invention to provide a gamma globulin preparation suitable for intravenous administration, in which **anticomplement** activity is less than about 0.1 C'50 units/mg.

SUMMARY:

BSUM(36)

According . . . has undergone no chemical or enzymatic modification, contains less than 0.1% IgA, essentially no IgM or aggregates and has an **anticomplement** activity of 0.1 or less C'50 units/mg. The immune gamma globulin preparation of the present invention consists of all the. . .

DETDESC:

DETD(34)

Anticomplement activity (ACA) is less than 0.10 C'50 units mg IgG as measured by a modified method of Kabet, E. A.. . .

DETDESC:

DETD(36)

In . . . was found to be stable for at least one year at both refrigeration and room temperatures with no change in **anticomplement** activity which averaged between 0.03 to 0.04 C'50 units/mg. No aggregates or fragments were detected.

DETDESC:

DETD(40)

Upon . . . found to be stable at room temperature for 6 months and at refrigeration temperatures for at least a year. The **anticomplement** activity did not change significantly from the initial levels and

1. 4,499,073, Feb. 12, 1985, Intravenously injectable immune serum globulin; Robert A. Tenold, 424/159.1, 167.1; 177.1; 514/21; 530/389.4, 389.5, 390.5, 831 [IMAGE AVAILABLE]

US PAT NO: 4,499,073 [IMAGE AVAILABLE]   L7: 1 of 2

ABSTRACT:
A composition is disclosed which comprises a solution in a pharmaceutically acceptable carrier of an immune serum globulin, said solution having an ionic strength and a pH to maintain the monomer content and the actual and latent anticomplement activity of the immune serum globulin such that the composition is intravenously injectable. Novel methods are disclosed for preparing the above composition.

530/388.1, 388.25, 388.4, 390.1 [IMAGE AVAILABLE]

US PAT NO: 5,159,064 [IMAGE AVAILABLE]   L2: 6 of 24

ABSTRACT:
Antibodies, including monoclonal antibodies (Mabs), can be made
substantially free of infectious viruses by storing them in a liquid
state at conditions of pH, temperature and time sufficient to inactive
substantially all infectious viruses. Preferred inactivation methods
involve use of a pH equal to or less than about 4.0 at a temperature of
at least about 5.degree. C. for at least about 16 hours.

8. 5,128,149, Jul. 7, 1992, Enhanced blood product antiviral process and
product produced; Edward Shanbrom, 424/529, 530, 533; 435/2 [IMAGE
AVAILABLE]

US PAT NO: 5,128,149 [IMAGE AVAILABLE]   L2: 8 of 24

ABSTRACT:
A transfusion blood product container for the introduction of one or more
blood products, such as whole blood, platelet concentrations, leukocyte
concentrations, plasma, phasma derivatives, whole blood fractions, and
combinations thereof, for transfusing the patient and an amount of one or
more glycyrrhizic triterpenoid compounds sufficient to comprise from 0.05
to 10.0 wt/%, preferably from about 0.5 to about 3 wt/%, of the contents
of the container when full of the blood product(s), sufficient to
substantially inactivate viruses contained in the blood product
introduced into said container is disclosed. One or more additional
products are added to the glycyrrhizic triterpenoid compounds to produce
a synergistic affect.

10. 4,948,877, Aug. 14, 1990, Preparation of retrovirus-free
immunoglobulins; Gautam Mitra, et al., 530/390.1; 424/176.1, 530;
435/236; 514/2 [IMAGE AVAILABLE]

US PAT NO: 4,948,877 [IMAGE AVAILABLE]   L2: 10 of 24

ABSTRACT:
Immune serum globulins (ISG) can be made substantially free of infectious
retroviruses by storing the ISG in a liquid state at conditions of pH,
temperature and time sufficient to inactivate substantially all
infectious retroviruses. Preferred inactivation methods involve use of
either of two specified storage conditions: (1) at a pH equal to or less
than about 4.25 at a temperature of about 27.degree. C. for at least 3
days, or (2) at a pH equal to or less than about 6.8 at a temperature of
about 45.degree. C. for at least about 8 hours.

14. 4,891,221, Jan. 2, 1990, Whole blood antiviral process and
composition; Edward Shanborm, 424/529; 435/2 [IMAGE AVAILABLE]

US PAT NO: 4,891,221 [IMAGE AVAILABLE]   L2: 14 of 24

ABSTRACT:
The treatment of blood to inactivate or destroy infective viruses found
in animal fluids and tissues, such as the cytomegalovirus, by mixing the
blood with an effective amount of glycyrrhizic tritepenoid compounds is
disclosed.

PAGE 284

8/7,K/1   (Item 1 from file: 653)
DIALOG(R)File 653:US Pat.Fulltext
(c) format only 1996 Knight-Ridder Info. All rts. reserv.

            01725325
Utility
REMOVAL OF LIPID SOLUBLE PROCESS CHEMICALS FROM BIOLOGICAL MATERIALS BY
EXTRACTION WITH NATURALLY OCCURRING OILS OR SYNTHETIC SUBSTITUTES THEREOF
[THAT ARE NONFLAMMABLE, NONEXPLOSIVE, PHYSIOLOGICALLY TOLERABLE]

PATENT NO.:   4,789,545
ISSUED: December 06, 1988 (19881206)
INVENTOR(s):   Woods, Kenneth R., Sea Cliff, NY (New York), US (United States
               of America)
               Orme, Thomas W., Huntington Station, NY (New York), US (United
               States of America)
ASSIGNEE(s):   New York Blood Center, Inc , (A U.S. Company or Corporation)
               , New York, NY (New York), US (United States of America)
               [Assignee Code(s): 59413]
APPL. NO.:   6-846,374
FILED: March 31, 1986 (19860331)
FULL TEXT: 997 lines

                        ABSTRACT

A method of removing lipid soluble process chemicals from biological
materials containing the lipid soluble process chemicals comprising
bringing the biological materials containing the lipid soluble process
chemicals into contact with an effective amount of a naturally occurring
oil extracted from a plant or an animal or a synthetic compound of similar
chemical structure, agitating the resultant mixture, separating out an
upper-phase and a lower-phase by sedimentation and decanting the
upper-phase. The method is particularly useful for producing relatively
virus free physiologically acceptable plasma.

What is claimed is:

  1. A method of removing lipid soluble process chemicals from biological
materials comprising blood plasma and fractions thereof containing said
lipid soluble process chemicals, said lipid soluble process chemical being
a virus attenuating solvent having a high flash point, a detergent, or a
mixture thereof, comprising bringing said biological materials containing
said lipid soluble process chemicals into contact with an effective amount
of a naturally occurring oil extracted from a plant or an animal or a
synthetic compound of similar chemical structure so as to remove 80% or
more of said lipid soluble process chemicals, the oil being nonflammable,
nonexplosive, compatible with parenterally administered biologics and blood
derivatives and pharmaceutically and physiologically tolerable by a human,
agitating the resultant mixture, separating out an upper-phase and a
lower-phase by sedimentation or centrifugation and decanting the
upper-phase.

  2. A method according to claim 1, wherein said oil is selected from the
group consisting of soybean oil, safflower oil, ricin oil, cottonseed oil,
corn oil, peanut oil, olive oil, whale oil and cod liver oil.

  3. A method according to claim 1, wherein said lipid soluble process